No new matter is entered by any of these amendments. A marked-up version of the amendments to the specification and claims is included in the attachment captioned "Version with Markings to Show Changes Made for USSN 09/008,945".

Remarks

Interview with Examiner

The undersigned and Rodger Tate met with Examiner Naff on November 1, 2001. Applicant thanks the Examiner for granting an interview. The Examiner suggested that a declaration under 37 CFR §132 would overcome the rejections over Atala under 35 U.S.C. §102 if the inventors affirmed both that they were the inventors of the instant application and of the material disclosed in Atala. The Examiner further suggested amending claim 46 to recite that the inventive compositions are partially hardened before the step of introduction in claim 44. Claim 46 has been amended accordingly. The participants also discussed the meaning of anatomy, which was defined in various medical dictionaries as concerning the structure or morphology of an organism or a part of an organism, and its relation to the word "anatomic" as used in the claims. The prior art and 112 rejections were also discussed.

Rejections under 35 U.S.C. §112

The Examiner rejects claims 44-52 under 35 U.S.C. §112, first paragraph, as not being supported by the specification. Applicant respectfully disagrees. Claim 44 recites hardening a polymer into a three-dimensional open-lattice structure after introducing the polymer into an animal as part of a cell-polymeric composition. Page 2, lines 19-23, disclose that cells may be suspended in a hydrogel solution and injected into an animal in which the hydrogel hardens. Example 1 of the application, beginning on page 12, line 21, discloses the step of hardening being completed after introduction of the cell-polymeric composition into an animal, as recited in claim 44. Page 12, line 24-lines 38 discloses mixing calcium sulfate with 1% sodium alginate and chondrocytes and injecting the mixture into mice. Addition of the calcium to the mixture begins the process of hardening. However, the mixture remains sufficiently flowable to be injected through a needle. The mixture hardens *in vivo* to form a three-dimensional scaffold for

chondrocytes, as indicated at page 13, lines 20-22. Page 13, lines 3-4 disclose that the injection site is "firm to palpation, without apparent diffusion of the mixture" 24 hours after introduction of the cell-polymeric composition. Page 11, lines 16-17, also discloses hardening of a hydrogel after introduction into an organism.

Claims 25, 26, 28-35 and 37-43 are rejected under 35 U.S.C. §112, paragraph 2 as being indefinite. The Examiner finds that the term "anatomic shape" does not sufficiently define shapes that are anatomic and not anatomic. Applicant respectfully disagrees. Anatomy concerns the morphologic structure of an organism (*Stedman's Medical Dictionary*, 25th edition, 1990 Baltimore, MD: Williams and Wilkins, p 70). One skilled in the art would recognize that an anatomic shape is one that reflects the structure of a part of an organism. For example, page 12, line 10 discloses that the compositions of the invention can be molded into the shape of an ear.

The Examiner rejects claims 44-52 as being confusing and unclear. The Examiner states that the meaning and scope of "completing hardening after introduction of the composition into an animal" is unclear and lacks antecedent basis. Applicant submits that recitation of hardening in claim 44 provides sufficient antecedent basis. One skilled in the art would understand that hardening is not instantaneous. Page 12, line 29 discloses that a cell polymeric composition may remain liquid for 30-45 minutes, even after the introduction of calcium ions. Furthermore, the claim does not recite a sequence for the steps of introducing and hardening. By reciting that the step of hardening is completed after introduction, the claim indicates that whether a practitioner performs the actions that will cause the polymer to harden before or after performing the step of introducing, the scope of the claim includes both partial hardening before introduction and complete hardening after introduction.

The Examiner states that the meaning and scope of "hardening is initiated before the step of introducing" in claim 46 is uncertain. Applicant respectfully disagrees. Nonetheless, claim 46 has been amended to recite that "hardening is initiated to partially harden the polymer before the step of introducing." Applicant submits that this clarifies that hardening may be initiated before introduction of the cell-polymeric composition into an animal and completed afterwards.

Applicant submits that claims 25, 26, 28-35 and 37-52 meet the requirements of 35 U.S.C. §112.

Rejections under 35 U.S.C. §102

The Examiner rejects claims 27-33, 36-42, and 44-51 under 35 U.S.C. §102 (a) and (f) as being anticipated by Atala. Applicant submits herewith declarations under 37 CFR 1.131 and 1.132. In the first, the inventors state that the invention was reduced to practice before the publication date of Atala. In the second, the inventors declare that they are the inventors of both the subject matter of the claims and the subject matter disclosed by Atala. Applicant submits that these declarations remove Atala as a reference. see MPEP 716.10 (attached to this Response).

Claims 25, 26, 28-35 and 37-43 stand rejected as being anticipated by Schlameus. The Examiner states that the capsules of Schlameus can be considered to be an anatomic shape. Applicant respectfully disagrees. Applicant submits that claims 25 and 35 require an shape that mimics a structure found in an organism. One skilled in the art would understand that the microcapsules of Schlameus do not fulfill this limitation. Applicant further submits that the Examiner's suggestion that the microcapsules of Schlameus could correspond to an anatomic shape is unsupported by the record and that the Examiner could not provide an example of such a structure. Further, Applicant notes that claims 25 and 35 recite a *continuous* three-dimensional open lattice structure. In contrast, column 12, lines 35-45 of Schlameus teach that the microcapsules are further suspended in an agarose matrix. Even where the microcapsules are directly implanted into an animal, as in Example 5 of Schlameus, the implant is a mass of microcapsules, not a continuous three-dimensional open lattice structure, as recited in claims 25 and 35. Applicant further notes that claims 28-34 depend from both claim 25 and 27 and that claims 37-43 depend from both 35 and 36. Neither claim 27 nor claim 36 has been rejected over Schlameus. Applicant submits that claims 25, 26, 28-35, and 37-43 are patentable in view of Schlameus.

Rejections under 35 U.S.C. 103

Claims 25, 26, 28-35, and 37-43 stand rejected as obvious over Atala in view of Nevo and Vacanti A and further in view of Vacanti B. Applicant submits that the declarations executed by the inventors remove Atala as a reference. Applicant submits that claims 25, 26, 28-35, and 37-43 are patentable in view of Nevo, Vacanti A, and Vacanti B, whether considered separately or in combination.

Claims 27-33, 36-43, and 44-52 stand rejected under as obvious over Schlameus in view of Barry and Dionne and further in view of Bhatnagar. Schlameus teaches hardening an alginate hydrogel before implanting it in an animal. Column 8, lines 28-30 disclose that the microcapsules are collected in a calcium chloride bath. The calcium diffuses into the capsules, hardening the alginate. Instead of remedying the failure of Schlameus to teach hardening a hydrogel at least partially *in vivo*, both Barry and Dionne teach away from the subject matter of the invention. The invention provides means for delivering cells into an organism to promote the development of tissue similar to naturally occurring tissue (page 2, lines 11-19). A tissue is "a collection of similar cells and the intercellular substances surrounding them," (*Stedman's Medical Dictionary*, p. 1603). Both Barry and Dionne teach against tissue development. Barry teaches an implant that is resorbed without being replaced by endogenous tissue (column 3, lines 64-66); Dionne teaches that cells should be immunoisolated (page 17, line 6) and that cell proliferation should be *inhibited* (page 18, lines 7-18). The hydrogel precursor solution disclosed at page 18, lines 20-21 is specifically recommended for inhibiting cell proliferation. In contrast, the present application provides a method for engraftment of an implant (page 2, line 16). There is no motivation to combine these references with Schlameus to produce a hydrogel construct that *promotes* tissue formation, as recited by claims 27, 36, and 44.

Bhatnagar fails to remedy the failure of Schlameus, Barry, and Dionne to suggest the claimed subject matter. Bhatnagar discloses a method of promoting cell differentiation and tissue formation by seeding cells onto a substrate grafted with peptides. Even if this teaching rendered it obvious to try to free the cells of Schlameus from their capsules, it provides no expectation of successful tissue generation. Schlameus teaches that the rate of release of the cells should be carefully controlled (column 4, lines 67-69). If the peptides of Bhatnagar are omitted from the gel, there is no indication that the cells will continue to exhibit the desired metabolic behavior when they are no longer encapsulated. Applicant submits that claims 27-33, 36-43, and 44-52 are patentable in view of Schlameus, Barry, Dionne, and Bhatnagar, whether considered separately or in combination. Applicant further notes that claims 28-33 and 37-43 depend from claims 25 and 35, respectively as well as claims 27 and 36.

Claims 25, 26, 28-35, and 37-43 stand rejected as obvious over Schlameus in view of Nevo and Vacanti A and further in view of Vacanti B. Applicant submits that the disclosure of

shapes other than microcapsules does not render obvious an anatomic shape for a hydrogel, as recited in claims 25 and 35. Nevo fails to disclose a hydrogel. Instead, Nevo discloses that a thrombin gel is pressed into the injured site (column 13, lines 60-61). Such a gel has not been molded into an anatomic shape *prior* to implantation. Neither Vacanti A nor Vacanti B discloses molding a polymer *gel*. Even if it were obvious to attempt to mold a hydrogel, the Vacanti references do not provide any expectation of success. Both references emphasize the importance of cell attachment to fibers. Vacanti A discloses, at column 5, lines 24-28, that without cell attachment, dissociated cells may "have difficulty...functioning." Vacanti A further discloses that tissue formation was not observed *in vivo* in areas injected with chondrocytes in suspension (column 10, lines 11-13). Vacanti B discloses (page 7) that ordinarily, tissue should not be implanted in volumes greater than 1 to 3 μL because, at greater volumes, the diffusion distance is too large for proper nutrition. Instead, Vacanti B discloses the use of porous branching fiber networks or monolayers of cells seeded on disks to enable nutrients to reach cells. The branching networks increase surface area along with volume. One skilled in the art would not have expected that the macroscopic compositions of the invention (see, for example, the ear disclosed at page 12, line 10), would have been able to permit proper nutrition for normal cell metabolism and tissue formation. Applicant submits that claims 25, 26, 28-35, and 37-43 are patentable in view of Schlameus, Nevo, Vacanti A, and Vacanti B, whether considered separately or in combination. Applicant further notes that claims 28-34 and 37-43 depend from claims 27 and 36, respectively, as well as claims 25 and 35.

In light of the foregoing Amendment and Remarks, Applicant respectfully submits that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

A Petition for Extension of Time Under 37 C.F.R. §1.136 is included herewith. Please charge the Petition fee of $920 (in view of the large entity status), and/or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,

Valarie B. Rosen
Registration Number 45,698

CHOATE, HALL & STEWART
Exchange Place
53 State Street
Boston, MA 02109
(617) 248-5000
Dated: January 29, 2002
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Additions are underlined and deletions are enclosed in brackets.

In the claims

27. A method for introducing cells into an animal to form tissue, comprising:

forming a cell-polymeric composition by mixing dissociated cells with a solution of a biodegradable, biocompatible natural or synthetic organic polymer;

introducing said cell-polymeric composition into the animal; and

following the step of introducing, hardening the polymer into a three-dimensional open-lattice structure which entraps water molecules to form a hydrogel containing the dissociated cells.

35. An implant for introducing cells into an animal, said implant being a cell-polymeric composition comprising: dissociated cells and a biodegradable, biocompatible natural or synthetic organic polymer, wherein the polymer hardens into a continuous three-dimensional open-lattice structure which entraps water molecules to form a hydrogel construct containing said dissociated cells, said hydrogel construct having a desired anatomic shape.

36. An implant for introducing cells into an animal to form tissue, said implant being a cell-polymeric composition comprising: dissociated cells and a biodegradable, biocompatible natural or synthetic organic polymer, wherein the polymer hardens into a three-dimensional open-lattice structure which entraps water molecules to form a hydrogel construct containing said dissociated cells, said cell-polymeric composition being suitable for implantation into an animal before hardening.

44. A method for introducing cells into an animal to form tissue, comprising:

forming a cell-polymeric composition by mixing dissociated cells with a solution of a biodegradable, biocompatible natural or synthetic organic polymer;

introducing said cell-polymeric composition into the animal; and

hardening the polymer into a three-dimensional open-lattice structure which entraps water molecules to form a hydrogel construct in which the dissociated cells are uniformly distributed,

wherein the step of hardening is completed after introduction of said cell-polymeric composition into the animal.

46. The method of claim 44, wherein the step of hardening is initiated to partially harden the polymer before the step of introducing.

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